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Editorial

HYPOGLYCEMIA AND THE RISK OF CARDIOVASCULAR EVENTS: CAUSALITY OR (JUST) AN EPIDEMIOLOGICAL ASSOCIATION?!

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On 6th of February 2008, the National Heart, Lung, and Blood Institute (NHLBI) issued a press release announcing that the intensive glucose-lowering arm of the ongoing Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was stopped earlier because of an excess number of deaths compared to the standard therapy arm, with a difference of 3 per 1000 participants per year during a mean follow-up of 3.5 years. These findings raised a lot of concerns regarding the safety of targeting a tight glycemic control (HbA1c<6%) and hypoglycemia requiring assistance was one of the suspected explanations for this excess in all-cause mortality [1]. A retrospective epidemiological analysis of the ACCORD study confirmed that severe hypoglycemia episodes (SHE) were associated with an increased risk of death in both study arms, but concluded that SHEs do not appear to account for the difference in mortality. Only one death out of the total of the 451 deaths occurring in the two arms of the study was adjudicated as definitely related to hypoglycemia [2].

Nevertheless, the relationship between hypoglycemia, mainly SHE, and negative outcomes (with focus on cardiovascular (CV) events and mortality, and all-cause mortality) started to be more carefully scrutinized by scientific researchers and avoidance of hypoglycemia has been included in all diabetes guidelines among the targets set for the management of hyperglycemia.

Definition and frequency of hypoglycemia in diabetes

Iatrogenic hypoglycemia is defined as a decrease in glucose level below a threshold that puts the patient at risk. According to the American Diabetes Association (ADA), hypoglycemia is classified into three levels: level 1- glucose concentration <70 mg/dL (3.9 mmol/L) but ≥54 mg/dL (3.0 mmol/L); level 2- glucose concentration <54 mg/dL (3.0 mmol/L); level 3- a severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery [3].

Reported frequency of hypoglycemia in type 2 diabetes mellitus (T2DM) varies widely according to the characteristics of studied populations (e.g. age, duration of diabetes, type of antihyperglycemic medications, or

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presence/absence of renal and other organ dysfunctions). In a meta-analysis, which included population-based studies published before 2015 on 532,542 people with T2DM oral therapies and insulin, the reported prevalence of hypoglycaemia was of 45% for mild/moderate episodes and 6% for severe episodes, with an incidence of 19.0 mild/moderate episodes per person-year and 0.80 of severe episodes, respectively. The prevalence and incidence were higher in patients treated with regimens including insulin and sulphonylureas [4]. In a more contemporary real world investigation in Canada, which included adults (≥18 years old) with type 1 diabetes mellitus (T1DM) or T2DM treated with insulin and/or insulin secretagogues, the incidence proportion and the rate of non-severe events in T2DM were 54% and, respectively, 28.0 events per person-year. SHE had an average rate of 2.5 events per person-year in the overall sample [5].

Hypoglycemia and CV events- are there pathophysiological links?

The proposed mechanisms linking hypoglycemia to possible deleterious effects on CV system include the sympathoadrenal response to low blood glucose levels with the release of epinephrine which can induce rhythm abnormalities and heart rate variability, as well as hemodynamic changes with increased heart workload, contractility and output. During episodes of hypoglycemia, there is a release of pro-inflammatory cytokines (C-reactive protein, vascular endothelial growth factor, and interleukin 6) and an increase in blood coagulation through increased macrophage and platelet activation and release of factor VIII. Hypoglycemia is also accompanied by an activation of the renin–angiotensin system, increased plasma aldosterone level and activation of the mineralocorticoid receptor that might exacerbate endothelial dysfunction [6].

Some of these mechanisms were confirmed in studies on humans in experimental or real-life conditions. During a hyperinsulinemic hypoglycemic clamp in a study on healthy subjects, a slight amplification of the R wave, a decrease in the ST segment and a remarkable flattening of the T wave as well as a slight prolongation of the QT interval were demonstrated [7]. In a study which included twenty-five insulin-treated patients with T2DM at increased CV risk, a simultaneous continuous interstitial glucose monitoring and ambulatory electrocardiogram monitoring were performed. Bradycardia and atrial and ventricular ectopic episodes were three to eightfold higher during nocturnal hypoglycemia compared with euglycemia, whereas during daytime hypoglycemia only ventricular ectopic episodes were significantly more frequent [8].

Does severe hypoglycemia cause CV events or is it just an epidemiological association?

Numerous randomized clinical trials and epidemiological studies found a robust association between SHE and incident major CV events and mortality, as well as all-cause deaths but this association was not found for non-severe hypoglycemia [5]. One of the most recent reports was published from the Veterans Affairs Diabetes Trial (VADT) in a post-hoc analysis [8]. SHE within the prior 3 months was associated with a 90% increased risk for composite CV outcome, a 3.7-fold risk of CV death, and 2.4 higher risk for all-cause mortality. Severe hypoglycemia occurring earlier (4–6 months prior) was not independently associated with risk for CV adverse events or death. The association of SHE with CV events or mortality was similar in the intensive and in the standard treatment groups, whilst the association with all-cause mortality was significantly greater in the standard versus the intensive treatment group

(hazard ratio [HR] 6.7 vs. 0.92, respectively; P = 0.019 for interaction). This latter finding was also seen in the ACCORD and ORIGIN trials suggesting that SHEs occurring in patients with suboptimal glycemic control carry an additional risk.

The association between SHE and CV risk can be explained by either a direct causal relationship or by common confounders (such as frailty), or even by reverse causality. This hypothesis has been recently investigated using data from the Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS) [9]. When the association between SHEs and subsequent CV or hospitalization for heart failure (hHF) events or death was examined in an unadjusted analysis, SHEs were significantly associated with a subsequent 4-point MACE, all-cause death, and CV death and the associations remained significant after adjustment for clinical and demographic characteristics (randomized treatment, age, gender, race, weight, and smoking). In the full-adjusted analysis for all baseline variables that were significantly associated with CV events, no association was found between SHEs and the above-mentioned outcomes. No associations were identified between SHEs and other types of subsequent CV events such as fatal/nonfatal myocardial infarction (MI), hospitalization for unstable angina, fatal/nonfatal stroke, or hHF in any of the models. On the other hand, the inverse association between a nonfatal CV event or hospitalization for unstable angina, nonfatal MI, nonfatal stroke, hHF and subsequent SHEs was statistically significant in all models, including the adjustment for a wider range of baseline variables. The authors concluded that "the bidirectional relationship between SHEs and CV outcomes suggests that there may be a common "frail" T2DM phenotype that is susceptible to both of these events. Thus, SHEs, rather than being causative of MACE, hHF, or all-cause death events, may simply be indicative of patients with a frail T2DM phenotype that are at high risk of both outcomes, likely due to a multitude of coexisting risk factors [9]."

This concept of the "frail" T2DM phenotype, which may mediate the association between SHEs and negative CV outcomes, was further validated using data from participants in the Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL). When subjects having a CV event after a SHE were examined, it was found that the association in full-adjusted model was significant only for all-cause deaths and CV deaths and non-significant for MACE and its individual components. Conversely, when the analysis was done for subjects having a SHE after a CV event, the association was significant and robust in all the models [10].

These two reports suggest that the "frail" T2DM phenotype, characterized by older age, longer diabetes duration, lower glomerular filtration rate and, more frequently, non-White, insulin treated, and had prior CV or heart failure events, increased susceptibility for both SHEs and CV events [9,10].

Not all authors would agree with such an explanation. It is the case of a meta-analysis published in 2016, on 19 studies, that presented the relationship between hypoglycemia and major adverse CV events, including all-cause mortality, CV deaths and nonfatal CV events, MI, stroke, revascularization, and coronary heart disease. The overall HR for the association between hypoglycemia and adverse vascular events was 1.9, with a high degree of heterogeneity among selected studies [11]. A dose-dependent relationship between hypoglycemia severity and adverse CV events was also suggested by a higher pooled risk ratio for severe hypoglycemia than for mild hypoglycemia (HR 2.33 vs. 1.68). Using the

statistical method of the bias analysis, it was shown that if there was an unmeasured parameter to explain the association, other than causality, this unmeasured parameter required a prevalence of 10% and a risk ratio of 10 to fully account for the association between hypoglycemia and adverse CV events. The authors concluded that the above observations were unlikely to have resulted from unmeasured confounding parameters; therefore the causality must be accepted.

Instead of conclusions

The epidemiological association between hypoglycemia, in particular serious hypoglycemia, and incident CV events is a confirmed fact. Whether it is a causal relationship or just a bi-directional association explained by a "frail" phenotype of T2DM, it is still a matter of debate. Nevertheless, avoidance of hypoglycemia remains a target of antihyperglycemic strategies while efforts to attain and maintain individualized glucose targets should be done from the time of diagnosis and throughout all DM duration.

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